PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Elizabeth A. Wayner Attorney Docket No: CYTE-1-6162

Serial No: 07/814,873

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Title (Amended): INHIBITION OF LYMPHOCYTE ADHERENCE TO VASCULAR ENDOTHELIUM

INFORMATION DISCLOSURE STATEMENT

Seattle, Washington 98101

July 1, 1992

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Applicant is aware of the information listed in the attached form that may be material to the prosecution of the above-identified continuation-in-part patent application. Copies of the listed documents, which are of record in the parent application (Serial No. 07/402,389), are enclosed.

A/A1. Rudslahti et al. describes a method for detaching cultured cells from the substratum using peptides from fibronectin containing the Arg-Gly-Asp (RGD) tripeptide.

A14. Hession et al., 1990, discusses α4β1 (i.e., VLA4) at, e.g., page 26, line 19, to page 27, line 6.

1. Liao et al., 1989, reported that MOPC 315, IgA-secreting lymphoid cells, in addition to binding to the cell binding domain via an RGD interaction, bound preferentially to the carboxy-terminal heparin binding domain by an RGD-independent mechanism.

2. Wayner et al., 1988, relates to monoclonal antibodies that inhibit cell adhesion to collagen, fibronectin, and collagen and fibronectin.

3. Humphries et al., 1988, observed that neurons of the peripheral nervous system were able to extend neurites onto substrates bearing both the central cell-binding domain and the IIICS region of fibronectin.

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4. Wayner & Carter, 1987, reports experiments in which monoclonal antibody technology and affinity chromatography were used to identify four distinct classes of cell surface receptors for collagen and fibronectin in human fibrosarcoma tumor cells. Comparison of α and β receptor subunits indicates that β subunits were distinct among the classes.

5. Hemler et al., 1987, relates to a monoclonal antibody (B-5G10) which recognizes the M_r 150,000/130,000 VLA-4 $\alpha 4\beta 1$ heterodimer complex and to crosslinking studies which indicated that the $\alpha 4$ subunit of VLA-4 is in noncovalent association with the β subunit. VLA-4 is demonstrated on the surface of lymphocytes.

6. Bernardi et al., 1987, reported that lymphoid precursor cells adhered to two different sites on fibronectin. The BaF3 cell line interacted with the RGD binding domain, whereas the PD31 cell line appeared to interact with a different domain located in the carboxy terminal segment and associated with a high affinity binding site for heparin.

7. Humphries et al., 1987, studies a series of overlapping synthetic peptides spanning the IIICS region. Two nonadjacent peptides, CS1 and CS5, were found to be competitively inhibitory for adhesion of fibronectin to melanoma, but not to fibroblastic, cells, with CS1 showing greater inhibitory activity than CS5.

8. Hynes, 1987, reviews the integrin family of cell surface receptors, including a4β1.

9. Humphries et al., 1986, compared the ability of fibronectin fragments to form adhesive interactions with melanoma versus fibroblastic cells. Fibroblastic BHK cells were observed to spread rapidly on a 75kDa fragment representing the RGDS containing cell-binding domain, whereas B16-F10 melanoma cells did not appear to spread on the 75kDa fragment, but, instead were observed to spread on a 113kDa fragment derived from the portion of the fibronectin containing the type III connecting segment (CS) difference region, or V-region (in which alternative splicing of mRNA may occur). In this IIICS region, located near the fibronectin carboxyl terminus, the sequence Arg-Glu-Asp-Val (REDV) appeared to have functional significance.

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10. Giancotti et al., 1986, reports that the interaction of hemopoietic cells with fibronectin involves the sequence Arg-Gly-Asp-Ser and a 145,000-D cell surface.

11. Kornblihtt et al., 1985, reports the primary structure of human fibronectin and analyzes the sequence for internal homologies and different binding domains.

12. Pierschbacher & Ruoslahti, 1984, reports that the ability of fibronectin to bind cells can be accounted for by the peptide L-arginyl-glycyl-L-aspartyl-L-serine (RGDS), a sequence which is part of the cell attachment domain of fibronectin and present in at least five other proteins.

A2. Jalkanen et al., 1986, is a review describing lymphocyte surface recognition elements for lymph node which are independent of interactions with mucosal high endothelial cells.

A3. Gallatin et al., 1983, is a review describing the evidence for two antigenically-distinct receptor specificities, one for peripheral lymph node high endothelial venules (HEV), and one for Peyer's patch HEV.

A4. Gallatin et al., 1986, describes that there are at least two independent homing receptors, one for peripheral nodes and another for Peyer's patches.

A5. Woodruff et al., 1987, is a review describing lymphocyte-HEV recognition mechanisms, and factors isolated from rat lymph using monoclonal antibodies termed HEBF-LN.

A6. Springer et al., 1987, is a review describing lymphocyte function-associated antigens LFA-1, CD2, and LFA-3 and presenting a hypothesis for involvement of LFA-1 in receptor-dependent and -independent adhesion in relation to extracellular matrix receptor family.

A7. Butcher et al., 1980, describes apparent preferential binding of lymphocytes to HEV in Peyer's patches and in lymph nodes, and proposes specific lymphocyte surface receptors for organ-restricted endothelial cell determinants.

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A8. Jalkanen et al., 1988, describes the Hermes-1 antigen involved in human lymphocyte-HEV interactions, as being an acidic sulfated molecule covalently modified by linkage of chondroitin sulfate and apparently processed from a precursor of 76kDA to either the 85- to 95-kDa form, or to a 180- to 200-kDa form.

A9. Carter & Wayner, 1988, describes a 90-kDa surface glycoprotein termed the class III collagen receptor (CRIII) and the definition of three domains using monoclonal antibodies.

A10. Haskard et al., 1986, describes inhibition of lymphocyte binding to endothelium with monoclonal antibodies to T lymphocyte surface antigens, and differences in binding to stimulated and unstimulated endothelium.

A11. Hamann et al., 1988, describes evidence for an accessory role of LFA-1 in lymphocyte high endothelium interaction during homing.

A12. Kupper et al., 1991, reports that the integrin-binding peptide GPEILDVPST abrogates T cell mediated immune responses *in vivo*. [By way of introduction, cell mediated contact hypersensitivity to haptens (e.g., trinitrochlorobenzene, TNCB) is well recognized as an *in vivo* immunologic method useful for evaluating the immunosuppressive activities of pharmaceutical agents.] At lines 15-17 of the Kupper et al. abstract, the Washington University authors report that: "T cells harvested from TCNB [sic] immune mice and treated with synthetic peptides GPEILDVPST or GRGDSP lose their ability to mediate this CHS [contact hypersensitivity] immune response in a murine model after cell transfer to syngenic recipients."

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A13. Springer, 1990, is a review of adhesion receptors of the immune system. Therein, at Table 1 and the related text, $\alpha 4$ is disclosed as associated with the $\beta 1$ subunit on human cells, and with the βp subunit on murine cells.

Respectfully submitted,

CHRISTENSEN, O'CONNOR,
JOHNSON & KINDNESS

Thomas F. Broderick
Registration No. 31,332

I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on July 1, 1992.

Date: July 1, 1992 Trisha Mitchell

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2800 PACIFIC FIRST CENTRE
1420 FIFTH AVENUE
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